Docket No. 44657-AAA-PCT-US/JPW/GJG/BJA

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant : Joseph R. Berger

Serial No.: 10/052,961 Group Art Unit: 1617

Filed : January 18, 2002 Examiner: S. Wang

Title : A METHOD FOR AMELIORATING MUSCLE WEAKNESS/WASTING IN A PATIENT INFECTED WITH HUMAN IMMUNODEFICIENCY VIRUS-TYPE 1

1185 Avenue of the Americas
New York, New York 10036

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

DECLARATION UNDER 37 C.F.R. §1.132 OF FAITH OTTERY, M.D., PH.D., FACN

I hereby declare that:

1. I am Senior Director, Medical Affairs, at Savient Pharmaceuticals, which is the owner of the above-identified application.

2. I am familiar with the selection and manufacture of unit dosage forms of oxandrolone. The 10mg unit dosage form of oxandrolone is approved for promoting weight gain after weight loss following chronic infection, such as HIV infection (for example, for prescribing information see Exhibit A).

3. I am familiar with the specification of the above-identified application, and with each of Metcalf et al., *Metabolism,*

14(1):59-66 (1965) ("Metcalf"), the description of ANAVAR® and U.S. Patent No. 5,073,380 issued to Babu et al., collectively "the cited combination of prior art."

4. I have read the November 15, 2007 Office Action issued in connection with the above identified application. The November 15, 2007 Office Action relies primarily on Metcalf to conclude that a 10mg unit dosage form would be obvious. I disagree with this conclusion in the November 15, 2007 Office Action.

5. In my experience the nitrogen-retention ratio, as proposed by Metcalf, has not been validated as a standard to be indicative of muscle mass change generally, or in HIV patients specifically. Nitrogen retention as used by Metcalf is a complex interplay of a number of variables and is not necessarily indicative of muscle mass or of muscle strength. It is therefore unpredictable based on Metcalf whether the "optimum" dose for maximum "nitrogen sparing" with oxandrolone of 25-30mg per day would be the optimum dose for ameliorating muscle weakness or wasting in a patient such as an HIV patient.

6. Even if one ignores the fact that Metcalf is not directly relevant to promoting weight gain per se or weight gain specifically in HIV patients, Metcalf and the cited combination of prior art can be reasonably only interpreted to suggest a 25-30mg unit dosage form for oxandrolone.

7. Those in the art are aware of "pill-burden" issues as related to patient-compliance (adherence) in chronic conditions. These issues are especially important in

patients being treated for HIV with multiple tablets. Consequently, those in the art are motivated to formulate treatments that minimize the number of tablets a patient needs to take each day. Generally, pill-burden concerns and patient-compliance issues both argue against splitting dosing into multiple tablets.

8. Therefore, one of skill in the art aware of the art-recognized issues of pill-burden and patient-compliance would understand Metcalf to suggest unit dosage forms of 25-30mg of oxandrolone. Nothing in Metcalf, the cited combination of prior art, or the November 15, 2007 Office Action provides any rationale to split and how to split the 25-30mg optimum daily dose proposed by Metcalf for nitrogen retention. In particular, I find no reason in Metcalf and the cited combination of prior art to make a 10mg unit dose form of oxandrolone instead of a 25-30mg unit dose form or yet some other dose form.

9. In addition, Grunfeld et al. (1986), a copy of which is attached hereto as **Exhibit B**, shows that administration of a single 20mg oxandrolone tablet per day to HIV patients was statistically similar to placebo results in treating weight loss in HIV patients: "[o]nly the gain in weight at the 40-mg dose of oxandrolone and the gain in BCM at the 40- and 80-mg doses of oxandrolone were greater than those in the placebo group" (see Abstract, page 304). The results in Grunfeld et al. show that unit dosage forms have unpredictable effects - a 20mg unit dose of oxandrolone did not work, yet the 10mg unit dose form is approved as set forth in paragraph 2 above. A person familiar with unit dose

formulation, therefore, could not predict from Metcalf and the cited combination of prior art which unit dosage form of oxandrolone would be effective to treat a given condition.

I hereby declare that all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements are made with the knowledge that any such willful false statement and the like so made is punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that any such willful false statement may jeopardize the validity of the application or any patent issuing thereon.

Date: 5/15/08

Faith D. Ottery MD

Faith D. Ottery, MD, PhD

EXHIBIT A

Rx only

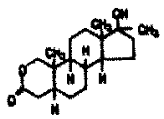
SAVIENT PHARMACEUTICALS, INC.

Oxandrin®(oxandrolone tablets, USP)CIII

DESCRIPTION

Oxandrin® oral tablets contain 2.5 mg or 10 mg of the anabolic steroid oxandrolone.

Oxandrolone is 17β-hydroxy-17α-methyl-2-oxa-5α-androstan-3-one with the following structural formula:



Inactive ingredients include cornstarch, lactose, magnesium stearate, and hydroxypropyl methylcellulose.

CLINICAL PHARMACOLOGY

Anabolic steroids are synthetic derivatives of testosterone. Certain clinical effects and adverse reactions demonstrate the androgenic properties of this class of drugs. Complete dissociation of anabolic and androgenic effects has not been achieved. The actions of anabolic steroids are therefore similar to those of male sex hormones with the possibility of causing serious disturbances of growth and sexual development if given to young children. Anabolic steroids suppress the gonadotropic functions of the pituitary and may exert a direct effect upon the testes.

During exogenous administration of anabolic androgens, endogenous testosterone release is inhibited through inhibition of pituitary luteinizing hormone (LH). At large doses, spermatogenesis may be suppressed through feedback inhibition of pituitary follicle-stimulating hormone (FSH).

Anabolic steroids have been reported to increase low-density lipoproteins and decrease high-density lipoproteins. These levels revert to normal on discontinuation of treatment.

In a single dose pharmacokinetic study of Oxandrin in elderly subjects, the mean elimination half-life was 13.3 hours. In a previous single dose pharmacokinetic study in younger volunteers, the mean elimination half-life was 10.4 hours. No significant differences between younger and elderly volunteers were found for time to peak, peak plasma concentration or AUC after a single dose of Oxandrin. The correlation between plasma level and therapeutic effect has not been defined.

INDICATIONS AND USAGE

Oxandrin is indicated as adjunctive therapy to promote weight gain after weight loss following extensive surgery, chronic infections, or severe trauma, and in some patients who without definite maintain normal weight, to offset the protein catabolism associated with prolonged administration of corticosteroids, and for the relief of the bone pain frequently accompanying osteoporosis (See **DOSAGE AND ADMINISTRATION**).

DRUG ABUSE AND DEPENDENCE

Oxandrolone is classified as a controlled substance under the Anabolic Steroids Control Act of 1990 and has been assigned to Schedule III (non-narcotic).

CONTRAINDICATIONS

1. Known or suspected carcinoma of the prostate or the male breast.
2. Carcinoma of the breast in females with hypercalcemia (androgenic anabolic steroids may stimulate osteolytic bone resorption).
3. Pregnancy, because of possible masculinization of the fetus. Oxandrin has been shown to cause embryotoxicity, fetotoxicity, infertility, and masculinization of female animal offspring when given in doses 9 times the human dose.
4. Nephrosis, the nephrotic phase of nephritis.
5. Hypercalcemia.

WARNINGS

PELIOSIS HEPATIS, A CONDITION IN WHICH LIVER AND SOMETIMES SPLENIC TISSUE IS REPLACED WITH BLOOD-FILLED CYSTS, HAS BEEN REPORTED IN PATIENTS RECEIVING ANDROGENIC ANABOLIC STEROID THERAPY. THESE CYSTS ARE SOMETIMES PRESENT WITH MINIMAL HEPATIC DYSFUNCTION, BUT AT OTHER TIMES THEY HAVE BEEN ASSOCIATED WITH LIVER FAILURE. THEY ARE OFTEN NOT RECOGNIZED UNTIL LIFE-THREATENING LIVER FAILURE OR INTRA-ABDOMINAL HEMORRHAGE DEVELOPS. WITHDRAWAL OF DRUG USUALLY RESULTS IN COMPLETE DISAPPEARANCE OF LESIONS. LIVER CELL TUMORS ARE ALSO REPORTED. MOST OFTEN THESE TUMORS ARE BENIGN AND ANDROGEN-DEPENDENT, BUT FATAL MALIGNANT TUMORS HAVE BEEN REPORTED. WITHDRAWAL OF DRUG OFTEN RESULTS IN REGRESSION OR CESSATION OF PROGRESSION OF THE TUMOR. HOWEVER, HEPATIC TUMORS ASSOCIATED WITH ANDROGENS OR ANABOLIC STEROIDS ARE MUCH MORE VASCULAR THAN OTHER HEPATIC TUMORS AND MAY BE SILENT UNTIL LIFE-THREATENING INTRA-ABDOMINAL HEMORRHAGE

THAT ARE KNOWN TO BE ASSOCIATED WITH INCREASED RISK OF ATHEROSCLEROSIS ARE SEEN IN PATIENTS TREATED WITH ANDROGENS OR ANABOLIC STEROIDS. THESE CHANGES INCLUDE DECREASED HIGH-DENSITY LIPOPROTEINS AND SOMETIMES INCREASED LOW-DENSITY LIPOPROTEINS. THE CHANGES MAY BE VERY MARKED AND COULD HAVE A SERIOUS IMPACT ON THE RISK OF ATHEROSCLEROSIS AND CORONARY ARTERY DISEASE.

Cholestatic hepatitis and jaundice may occur with 17-alpha-alkylated androgens at a relatively low dose. If cholestatic hepatitis with jaundice appears or if liver function tests become abnormal, oxandrolone should be discontinued and the etiology should be determined. Drug-induced jaundice is reversible when the medication is discontinued.

In patients with breast cancer, anabolic steroid therapy may cause hypercalcemia by stimulating osteolysis. Oxandrolone therapy should be discontinued if hypercalcemia occurs.

Edema with or without congestive heart failure may be a serious complication in patients with pre-existing cardiac, renal, or hepatic disease. Concomitant administration of adrenal cortical steroid or ACTH may increase the edema.

In children, androgen therapy may accelerate bone maturation without producing compensatory gain in linear growth. This adverse effect results in compromised adult height. The younger the child, the greater the risk of compromising final mature height. The effect on bone maturation should be monitored by assessing bone age of the left wrist and hand every 6 months (See **PRECAUTIONS: Laboratory Tests**).

Geriatric patients treated with androgenic anabolic steroids may be at an increased risk for the development of prostatic hypertrophy and prostatic carcinoma.

ANABOLIC STEROIDS HAVE NOT BEEN SHOWN TO ENHANCE ATHLETIC ABILITY.

PRECAUTIONS

Concurrent dosing of oxandrolone with warfarin may result in unexpectedly large increases in the INR or prothrombin time (PT). When oxandrolone is prescribed to patients being treated with warfarin, doses of warfarin may need to be decreased level and diminish the risk of potentially serious bleeding (See PRECAUTIONS: Drug Interactions).

General:
Women should be observed for signs of virilization (deepening of the voice, hirsutism, acne, clitoromegaly). Discontinuation of drug therapy at the time of evidence of mild virilism is necessary to prevent irreversible virilization. Some virilizing changes in women are irreversible even after prompt discontinuance of therapy and are not prevented by concomitant use of estrogens. Menstrual irregularities may also occur.

Anabolic steroids may cause suppression of clotting factors II, V, VII, and X, and an increase in prothrombin time.

Information for patients:
The physician should instruct patients to report immediately any use of warfarin and any bleeding.
The physician should instruct patients to report any of the following side effects of androgens:
Males: Too frequent or persistent erections of the penis, appearance or aggravation of acne.
Females: Hoarseness, acne, changes in menstrual periods, or more facial hair.
All patients: Nausea, vomiting, changes in skin color, or ankle swelling.

Geriatric Use:
Oxandrin, at daily doses of 5 mg bid, and 10 mg bid, was evaluated in four clinical trials involving a total of 339 patients with different underlying medical conditions. The maximum duration of treatment was 4 months with the average duration of treatment from 68.5 days to 94.7 days across the studies. A total of 172 elderly patients (≥ 65 years of age) received Oxandrin treatment. Mean weight gain was similar in those ≥ 65 and those < 65 years of age. No significant differences in efficacy were detected between the 5 mg bid and 10 mg bid daily doses. The adverse event profiles were similar between the two age groups although the elderly, particularly in women, had a greater sensitivity to fluid retention and increases in hepatic transaminases. A single dose pharmacokinetic study in elderly volunteers revealed an increased half-life when compared to younger volunteers. (see CLINICAL PHARMACOLOGY) Based on greater sensitivity to drug-induced fluid retention and transaminase elevations, a lower dose is recommended in the elderly (see DOSAGE AND ADMINISTRATION).

Laboratory Tests:
Women with disseminated breast carcinoma should have frequent determination of urine and serum calcium levels during the course of therapy. (See **WARNINGS**).

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Exhibit A

because of the hepatotoxicity associated with the use of 17-alpha-alkylated androgens, liver function tests should be obtained periodically.

Periodic (every 6 months) x-ray examinations of bone age should be made during treatment of children to determine the rate of bone maturation and the effects of androgen therapy on the epiphyseal centers.

Androgenic anabolic steroids have been reported to increase low-density lipoproteins and decrease high-density lipoproteins. Therefore, caution is required when administering these agents to patients with a history of cardiovascular disease or who are at risk for cardiovascular disease. Serum determination of lipid levels should be performed periodically and therapy adjusted accordingly.

Hemoglobin and hematocrit should be checked periodically for polycythemia in patients who are receiving high doses of anabolic steroids.

Drug interactions

Anticoagulants:
Anabolic steroids may increase sensitivity to oral anticoagulants. Dosage of the anticoagulant may have to be decreased in order to maintain desired prothrombin time. Patients receiving oral anticoagulant therapy require close monitoring, especially when anabolic steroids are started or stopped.

Warfarin: A multidose study of oxandrolone, given as 5 or 10 mg bid in 15 healthy subjects concurrently treated with warfarin, resulted in a mean increase in S-warfarin half-life from 26 to 48 hours and AUC from 4.55 to 12.08 ng*hr/mL; similar increases in R-warfarin half-life and AUC were also detected. Microscopic hematuria (9/15) and gingival bleeding (1/15) were also observed. A 5.5-fold decrease in the mean warfarin dose from 6.13 mg/day to 1.13 mg/day (approximately 80-85% reduction of warfarin dose), was necessary to maintain a target INR of 1.5. When oxandrolone therapy is initiated in a patient already receiving treatment with warfarin, the INR or prothrombin time (PT) should be monitored closely and the dose of warfarin adjusted as necessary until a stable target INR or PT has been achieved. Furthermore, in patients receiving both drugs, careful monitoring of the INR or PT, and adjustment of the warfarin dosage if indicated are recommended when the oxandrolone dose is changed or discontinued. Patients should be closely monitored for signs and symptoms of occult bleeding.

Oral hypoglycemic agents:
Oxandrolone may inhibit the metabolism of oral hypoglycemic ...

Adrenal steroids or ACTH:
In patients with edema, concomitant administration with adrenal cortical steroids or ACTH may increase the edema.

Drug/Laboratory test interactions:
Anabolic steroids may decrease levels of thyroxine-binding globulin, resulting in decreased total T_4 serum levels and increased resin uptake of T_3 and T_4. Free thyroid hormone levels remain unchanged. In addition, a decrease in PBI and radioactive iodine uptake may occur.

Carcinogenesis, mutagenesis, impairment of fertility

Animal data:
Oxandrolone has not been tested in laboratory animals for carcinogenic or mutagenic effects. In 2-year chronic oral rat studies, a dose-related reduction of spermatogenesis and decreased organ weights (testes, prostate, seminal vesicles, ovaries, uterus, adrenals, and pituitary) were shown.

Human data:
Liver cell tumors have been reported in patients receiving long-term therapy with androgenic anabolic steroids in high doses (See **WARNINGS**). Withdrawal of the drugs did not lead to regression of the tumors in all cases.

Geriatric patients treated with androgenic anabolic steroids may be at an increased risk for the development of prostatic hypertrophy and prostatic carcinoma.

Pregnancy: Teratogenic effects-Pregnancy Category X (See **CONTRAINDICATIONS**).

Nursing mothers:
It is not known whether anabolic steroids are excreted in human milk. Because of the potential of serious adverse reactions in nursing infants from oxandrolone, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric use:
Anabolic agents may accelerate epiphyseal maturation more rapidly than linear growth in children and the effect may continue for 6 months after the drug has been stopped. Therefore, therapy should be monitored by x-ray studies at 6-month intervals in order to avoid the risk of compromising adult height. Androgenic anabolic steroid therapy should be used very cautiously in children and only by specialists who are aware of the effects on bone maturation (See **WARNINGS**).

ADVERSE REACTIONS

Patients with moderate to severe COPD or COPD patients who are unresponsive to bronchodilators should be monitored closely for COPD exacerbation and fluid retention.

The following adverse reactions have been associated with use of anabolic steroids:
Hepatic: Cholestatic jaundice with, rarely, hepatic necrosis and death. Hepatocellular neoplasms and peliosis hepatis with long-term therapy (See **WARNINGS**). Reversible changes in liver function tests also occur including increased bromsulfophthalein (BSP) retention, changes in alkaline phosphatase and increases in serum bilirubin, aspartate aminotransferase (AST, SGOT) and alanine aminotransferase (ALT, SGPT)
In males:
Prepubertal: Phallic enlargement and increased frequency or persistence of erections.
Postpubertal: Inhibition of testicular function, testicular atrophy and oligospermia, impotence, chronic priapism, epididymitis, and bladder irritability.
In females:
Clitoral enlargement, menstrual irregularities.
CNS: Habituation, excitation, insomnia, depression, and changes in libido.
Hematologic: Bleeding in patients on concomitant oral anticoagulant therapy.
Breast: Gynecomastia.
Larynx: Deepening of the voice in females.
Hair: Hirsutism and male pattern baldness in females.
Skin: Acne (especially in females and prepubertal males).
Skeletal: Premature closure of epiphyses in children (See **PRECAUTIONS: Pediatric use**).
Fluid and electrolytes: Edema, retention of serum electrolytes (sodium chloride, potassium, phosphate, calcium).
Metabolic/Endocrine: Decreased glucose tolerance (See **PRECAUTIONS: Laboratory tests**), increased creatinine excretion, increased serum levels of creatinine phosphokinase (CPK). Masculinization of the fetus. Inhibition of gonadotropin secretion.

OVERDOSAGE

No symptoms or signs associated with overdosage have been reported. It is possible that sodium and water retention may occur.

The oral LD_{50} of oxandrolone in mice and dogs is greater than 5,000 mg/kg. No specific antidote is known, but gastric lavage may be used.

DOSAGE AND ADMINISTRATION

Therapy with anabolic steroids is adjunctive to and not a replacement for conventional therapy. The duration of therapy with Oxandrin (oxandrolone) will depend on the response of the patient and the possible appearance of adverse reactions. Therapy should be intermittent.

Adults: The response of individuals to anabolic steroids varies. The daily adult dosage is 2.5 mg to 20 mg given in 2 to 4 divided doses. The desired response may be achieved with as little as 2.5 mg or as much as 20 mg daily. A course of therapy of 2 to 4 weeks is usually adequate. This may be repeated intermittently as indicated.
Children: For children the total daily dosage of Oxandrin is ≤0.1 mg per kilogram body weight or ≤0.045 mg per pound of body weight. This may be repeated intermittently as indicated.

Geriatric Use: Recommended dose for geriatric patients is 5 mg bid.

HOW SUPPLIED

Oxandrin 2.5 mg tablets are oval, white, and scored with BTG on one side and "11" on each side of the scoreline on the other side; bottles of 100 (NDC 54396-111-11).
Oxandrin 10 mg tablets are capsule shaped, white, with BTG on one side and "10" on the other side; bottles of 60 (NDC 54396-110-60).

R_x only Issued: January, 2006

Manufactured for
Savient Pharmaceuticals, Inc. by:

DSM Pharmaceuticals, Inc.
Greenville, NC 27834

Pfizer Co.
New York, NY 10017

Address medical inquires to:
Savient Pharmaceuticals, Inc.
One Tower Center
Fourteenth Floor
East Brunswick, NJ 08816
866-692-6374

Printed in USA

OXANDRIN®
(oxandrolone tablets, USP)CIII

SAVIENT

EXHIBIT B

Applicant: Joseph R. Berger
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Exhibit B

Oxandrolone in the Treatment of HIV-Associated Weight Loss in Men

A Randomized, Double-Blind, Placebo-Controlled Study

Carl Grunfeld, MD, PhD, Donald P. Kotler, MD,† Adrian Dobs, MD,‡ Marshall Glesby, MD,§ and Shalender Bhasin, MD,|| for the Oxandrolone Study Group*

Objective: To evaluate the efficacy and safety of oxandrolone in promoting body weight and body cell mass (BCM) gain in HIV-associated weight loss.

Methods: Randomized, double-blind, placebo-controlled trial. Two hundred sixty-two HIV-infected men with documented 10% to 20% weight loss or body mass index ≤ 20 kg/m^2 were randomized to placebo or to 20, 40, or 80 mg of oxandrolone daily. After 12 weeks, subjects were allowed to receive open-label oxandrolone at a dose of 20 mg for another 12 weeks.

Results: Body weight increased in all groups, including the group receiving placebo, during the double-blind phase (1.1 ± 2.7, 1.8 ± 3.9, 2.8 ± 3.3, and 2.3 ± 2.9 kg in placebo and 20-, 40-, and 80-mg oxandrolone groups, respectively; all $P < 0.014$ vs. baseline). BCM increased from baseline in all groups (0.45 ± 1.7, 0.91 ± 2.2, 1.5 ± 2.5, and 1.8 ± 1.8 kg in placebo and 20-, 40-, and 80-mg oxandrolone groups, respectively). At 12 weeks, only the gain in weight at the 40-mg dose of oxandrolone and the gain in BCM at the 40- and 80-mg doses of oxandrolone were greater than those in the placebo group, however. Oxandrolone treatment was associated with significant suppression of sex hormone–binding globulin, luteinizing hormone, follicle-stimulating hormone, and total and free testosterone levels. Treatment was generally well tolerated but accompanied by significant increases in transaminases and low-density lipoprotein as well as decreases in high-density lipoprotein.

Conclusion: Oxandrolone administration is effective in promoting dose-dependent gains in body weight and BCM in HIV-infected men with weight loss.

Key Words: wasting syndrome, cachexia, anabolic therapy, body composition, anabolic steroid, lean body mass, fat toxicity, liver function, lipoproteins, atherosclerosis

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From the *University of California, San Francisco, and the Department of Veterans Affairs Medical Center, San Francisco, CA; †St. Lukes-Roosevelt Medical Center, Columbia University School of Medicine, New York, NY; ‡Johns Hopkins School of Medicine, Baltimore, MD; §Community Research Initiative on AIDS, New York, NY and ||Charles Drew University of Medicine and Science, Los Angeles, CA.

Grant support provided by Biotechnology General (now Savient Pharmaceuticals).

Reprints: Carl Grunfeld, Metabolism section (111F), Department of Veterans Affairs Medical Center, 4150 Clement Street, San Francisco, CA 94121 (e-mail: grunfld@itsa.ucsf.edu).

Although the prevalence of weight loss in HIV-infected patients has decreased in developed nations with widespread use of antiretroviral drug therapy, weight loss continues to be a significant problem, affecting 31% of patients during the course of their illness.[1–4] In Africa and Asia, where most HIV-infected patients reside, weight loss is a major presenting feature of AIDS.[5] Weight loss and, in particular, loss of body cell mass (BCM) are independent risk factors for death in patients with HIV infection, even when the CD4 cell count and history of complications are taken into account.[5–11] Furthermore, loss of weight, lean body mass, and BCM are accompanied by decreased function, worsening quality of life (QOL), and increasing hospitalization rates.[12–15]

Early studies suggested that BCM was preferentially lost and fat spared in men with HIV-associated wasting.[16] Whereas some subsequent studies had similar findings,[8,17] other studies in men and women found more significant loss of fat.[18–21] An explanation for these discrepancies is that subjects who had a low percentage of fat when first studied lost predominantly lean body mass, whereas those who started with higher percentage fat lost predominantly fat.[20]

Nutritional therapy and appetite stimulants can promote weight gain in patients with HIV-associated wasting.[22–25] The predominant gain is in body fat, however. Although increased energy stores may reduce loss of BCM in future episodes of weight loss,[18] body fat stores do not correlate with survival.[6,8,9] In contrast, anabolic therapy with growth hormone (rhGH) has the potential of inducing gain of lean body mass; however, rhGH therapy also induces loss of fat reserves.[26–29]

Testosterone supplementation increases fat-free mass and muscle strength in HIV-infected men with mild to moderate weight loss.[30–37] Androgenic steroids promote a positive nitrogen balance and weight gain (or amelioration of weight loss) in other catabolic illnesses, including acute alcoholic hepatitis, cancer, end-stage renal disease, and burns.[38–51] In studies of small numbers of patients with HIV-associated wasting, orally administered androgens, such as oxandrolone and oxymetholone, and the parenterally administered androgen nandrolone decanoate have induced significant weight gain.[43–51] Given the potential advantage of an orally administered anabolic therapy, such as oxandrolone, we undertook a double-blind, placebo-controlled, randomized trial of graded doses of oxandrolone in HIV-infected subjects with weight loss, testing its effects on weight gain, body composition, total work capacity, health-related QOL, and safety.

METHODS

Signed informed consent was obtained from each patient before entry under protocols approved by the institutional review board at each participating center. This was a randomized, placebo-controlled, parallel-group, double-blind, multisite clinical trial conducted at 25 sites between September 25, 1996 and July 20, 1998.

Participants

Eligible subjects were HIV-infected men ≥18 years of age who had 10% to 20% unintentional weight loss from premorbid weight documented in medical records or a body mass index (BMI) ≤20 kg/m^2, a Karnofsky Performance Scale score >60%, a life expectancy of >6 months, and the ability to consume a normal well-balanced diet at entry as assessed by a dietitian. Therapy with antiretroviral medication was not required; however, subjects on antiretroviral therapy had to be on a stable regimen for more than 6 weeks at the time of entry.

Exclusion criteria included any opportunistic infection within 60 days of enrollment; loss of >5% body weight in the previous 30 days; chronic fever >101°F with a frequency ≥3 days per week for at least 2 weeks in the previous 30 days; aspartate aminotransferase (AST), alanine aminotransferase (ALT), or alkaline phosphatase levels greater than 5 times the upper limit of normal and/or bilirubin level ≥2.0 mg/dL within 2 weeks; serum creatinine >2.0 mg/dL; known impaired digestive or absorptive function; chronic uncontrolled diarrhea (>3 liquid stools per day at least 4 days per week for >2 weeks); current treatment with anticoagulants or oral hypoglycemic agents; or treatment with appetite stimulants, weight-promoting agents, anabolic steroids, or testosterone in the previous 4 weeks. This dose-ranging study did not include women, because it was not known whether doses of this magnitude would cause significant virilization in women.

Treatment Assignment and Randomization

Subjects were assigned in concealed randomization (1:1:1:1) balanced at each center to placebo (4 tablets) or to 20 mg/d of oxandrolone (1 20-mg tablet of oxandrolone and 3 placebos), 40 mg/d (2 20-mg tablets of oxandrolone and 2 placebos), or 80 mg/d of oxandrolone (4 20-mg oxandrolone tablets) provided by Savient Pharmaceuticals (East Brunswick, NJ [formerly Bio-Technology General, Corporation]). Investigators and patients were blinded to treatment assignment during the initial 12 weeks. After 12 weeks, all subjects who wished to continue were placed on 20 mg of oxandrolone in an open-label continuation.

Subject Accountability

Two hundred sixty-two patients were randomized and included in the intent-to-treat analysis (placebo [n = 65], 20 mg of oxandrolone [n = 64], 40 mg of oxandrolone [n = 65], and 80 mg of oxandrolone [n = 68]). Of these, 195 subjects completed the double-blind phase and 193 completed the open-label phase. Of the 67 subjects who discontinued treatment during the double-blind phase, 12 were in the placebo group, 18 were in the 20-mg oxandrolone group, 18 were in the 40-mg oxandrolone group, and 19 were in the 80-mg oxandrolone group. Reasons for discontinuations included adverse experience,[20] death,[6] intercurrent medical problem or disease-related complication,[2] subject relocation or voluntary patient withdrawal,[21] and noncompliance.[18]

Assessments

Measurements were made at baseline and at 2, 4, 8, and 12 weeks in the double-blind placebo phase and at weeks 14, 18, and 24 in the open-label study. The primary outcome was change in body weight measured at each time point under standardized conditions (at the same time, preferably in the morning, wearing only underwear and socks) on a single balance-type scale that had been recently calibrated by a state agent or third-party source. Other outcomes included measurement of fat and BCM by bioelectrical impedance analysis (BIA) (RJL Systems). Because changes in hydration status and technical aspects of performance affect BIA, data were excluded if the change in BCM was >2.5 times the change in weight or the change in BCM was >7.5 kg in a subject; 18 subjects were thus excluded from the body composition analysis because of quality control problems with BIA measurements (6 from placebo group, 3 from 20-mg oxandrolone group, 6 from 40-mg oxandrolone group, and 3 from 80-mg oxandrolone group). Health-related QOL was measured by the Medical Outcomes Study (MOS) HIV health survey.[52] Treadmill tests were performed at centers with treadmill capability on day 1 and at weeks 4 and 12. Changes in physical capacity were assessed by changes in total workload from the treadmill tests. Nineteen percent of subjects had treadmill tests performed at week 12. Total workload is defined as Σ[speed (m/min)] [% grade/100] [time in minutes on treadmill].

Safety assessments, including HIV RNA levels by reverse transcriptase polymerase chain reaction (RT-PCR), CD4 T-lymphocyte counts, complete blood cell counts, and blood chemistry, were measured at Covance Laboratories.

Serum luteinizing hormone (LH), follicle-stimulating hormone (FSH), and sex hormone–binding globulin (SHBG) as well as testosterone levels were measured by 2-site–directed immunofluorometric assays (Delfia-Wallac, Gaithersburg, MD), with sensitivities of 0.05 U/L, 0.15 U/L, and 6.25 nmol/L, respectively, as described previously.[53,54] The intra- and interassay coefficients of variation were 10.7% and 13.0% for LH, 3.2% and 11.3% for FSH, and 10.0% and 10.2% for SHBG, respectively. The cross-reactivity of free α-subunit and other pituitary hormones in the LH and FSH assays was <1%.

Serum total testosterone levels were measured using a radioimmunoassay (RIA) with an iodinated testosterone tracer[54,55] that has been validated against liquid chromatography–mass spectrometry tandem mass spectrometry. This assay has a sensitivity of 0.44 ng/dL and intra- and interassay coefficients of variation of 8.2% and 13.2%, respectively. Free testosterone levels were measured by a sensitive equilibrium dialysis method,[54,55] optimized to measure low concentrations with accuracy. Two hundred microliters of serum in the inner compartment was dialyzed against 2.4 mL of dialysis buffer that approximates the composition of a

protein-free ultrafiltrate of human serum. Dialysis was performed overnight for 16 hours at 37°C. Testosterone concentration in the dialysate was measured by RIA using ^{125}I-labeled testosterone. The sensitivity of the free testosterone assay is 0.6 pg/mL (2.0 pmol/L), with intra- and interassay coefficients of variation of 4.2% and 12.3%, respectively.

Total and free testosterone concentrations were not consistently changed during oxandrolone treatment despite suppression of LH concentrations, suggesting that oxandrolone or one of its metabolites might have cross-reacted in the testosterone assays. Therefore, we established a chromatographic system to separate testosterone from oxandrolone before RIA. Serum samples were extracted using ethyl acetate and hexane (3:2 vol/vol) and subjected to chromatography on celite columns equilibrated in isooctane. Lipemic samples were clarified by centrifugation before extraction. Testosterone was eluted by washing columns with 10% ethyl acetate in isooctane. In preliminary experiments, we demonstrated that >90% of ^{14}C-testosterone eluted with 10% isooctane, whereas >90% of ^{3}H-oxandrolone eluted with ≥15% iso-octane. Less than 5% of ^{14}C-oxandrolone eluted with 10% isooctane; conversely, less than 5% of testosterone eluted at isooctane concentrations ≥15%. Eluates were dried under nitrogen and taken up in assay buffer. Recovery of known amounts of testosterone added to charcoal-stripped serum samples during extraction and celite chromatography was consistently better than 80%. Therefore, values were not corrected for losses during chromatography.

At each visit, intercurrent illnesses, symptoms, and additional medicines were recorded. Compliance was assessed by pill count.

Statistics

Results are presented as mean ± standard deviation (SD). Primary efficacy end points were changes in body weight and body composition from baseline. Based on preliminary data, the study was designed to detect a 2.0-kg (SD = 3.5 kg) increase in oxandrolone-treated patients compared with patients treated with placebo with a power of 80%, under the presumption that those on placebo would, on average, lose weight during the course of the study. The study was not powered to detect significant changes in secondary end points, such as quality of life. Analysis of variance (ANOVA) and the Dunnett t test were used to analyze primary and secondary efficacy parameters. To control the overall type I error rate of 0.05 for the multiple comparisons, Bonferroni inequality was used; treatment differences were considered significant if the significance level for that comparison was <0.017 instead of 0.05. Within-treatment changes from baseline were tested using a 1-way t test. The number of patients with adverse events and discontinuations was compared using the Fisher exact test. The prevalence of World Health Organization (WHO) grade III and IV toxicities was compared with placebo using the χ^2 test, with differences across dosages analyzed by the Cochran-Armitage trend test. Demographic and disease history variables at baseline were compared between treatment groups using ANOVA. The effect of race was tested using the χ^2 test.

RESULTS

Subject Characteristics

Baseline characteristics of the subjects were not significantly different among treatment groups (Table 1). Seventy percent of participants were white, 17% were African American, 11% were Hispanic, and 2% were other. Weight loss before entry averaged 16.4% ± 8.0% from baseline.

Body Weight and Composition

In subjects who were evaluated at baseline and received drug, weight increased progressively in all groups, including the placebo group, during the study (Fig. 1A). A significant increase occurred as early as 2 weeks after baseline for each group, including the placebo group. On an intent-to-treat basis at 12 weeks or at last measurement during the double-blind placebo phase, for the 258 subjects with baseline weight (Table 2), there was a gain of 1.1 ± 2.7 kg on placebo, 1.8 ± 3.9 kg on 20 mg of oxandrolone, 2.8 ± 3.3 kg on 40 mg of oxandrolone, and 2.3 ± 2.9 kg on 80 mg of oxandrolone (all $P < 0.014$ vs. baseline). Weight gain at 2, 4, 8, and 12 weeks on the 40-mg dose of oxandrolone was statistically different from weight gain on placebo ($P = 0.0040$ vs. placebo at

TABLE 1. Baseline Characteristics of the Participants (N = 262)

	Placebo (n = 65)	Oxandrolone 20 mg (n = 64)	40 mg (n = 65)	80 mg (n = 68)
Age (y)	41.7 ± 8.4	41.1 ± 9.0	40.1 ± 7.5	39.5 ± 7.5
Height (in)	69.8 ± 3.0	69.8 ± 3.2	69.0 ± 3.0	70.0 ± 2.9
Weight (kg)	66.6 ± 9.9	65.9 ± 9.6	65.0 ± 11.1	65.4 ± 8.7
BMI (kg/m^2)	20.7 ± 2.7	21.0 ± 2.7	21.1 ± 3.2	20.6 ± 2.4
Weight loss* (% from baseline)	17.7 ± 6.7	15.8 ± 6.1	15.0 ± 7.2	16.9 ± 11.1
CD4$^+$ lymphocytes × 10^6/L	225 ± 188	226 ± 223	261 ± 211	252 ± 191
HIV PCR (log$_{10}$/mL)	5.31 ± 5.76	5.19 ± 5.58	5.19 ± 5.58	5.09 ± 5.59

*n = 59 for placebo, n = 62 for 20 mg of oxandrolone, n = 60 for 40 mg of oxandrolone, and n = 60 for 80 mg of oxandrolone; some subjects met entry criteria based on having a BMI ≤ 20 and did not have weight loss recorded.

Values are mean ± SD. There were no significant differences between the groups.

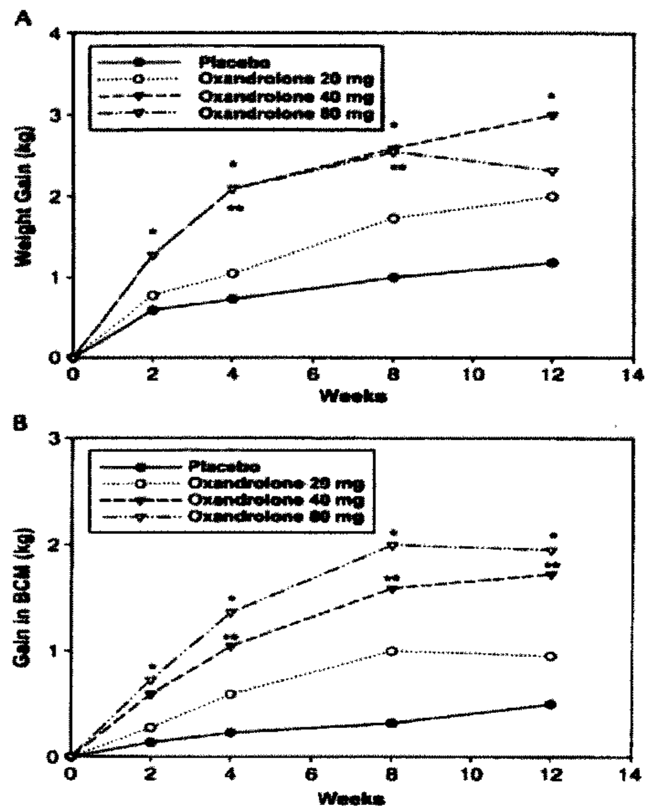

FIGURE 1. A, Average body weight gain during the 12-week treatment period. Mean change in weight from baseline at each time point is shown. Data are mean ± SD. **P* (40 mg of oxandrolone vs. placebo) < 0.017, ***P* (80 mg of oxandrolone vs. placebo) < 0.017. B, Average change in BCM during the 12-week treatment period. BCM was measured by BIA. Data are mean ± SD. **P* (40 mg of oxandrolone vs. placebo) < 0.017, ***P* (80 mg of oxandrolone vs. placebo) < 0.017.

12 weeks). The difference in weight gain between the 80-mg oxandrolone group and the placebo group was significant at 4 and 8 weeks but not at 2 or 12 weeks ($P = 0.045$ at 12 weeks, which did not meet the multiple comparisons criterion). There was no significant effect of performance site.

Body composition was measured by using BIA. Thirty patients at 4 centers underwent dual energy x-ray absorptiometry (DEXA) measurements to validate body composition measurements by BIA. The correlation between the measurements of fat-free mass by the 2 methods was 0.937 ($P < 001$).

BCM increased progressively and significantly in all groups (see Fig. 1B). At 12 weeks or last visit on an intent-to-treat basis, the increase in BCM was 0.45 ± 1.7 kg on placebo, 0.91 ± 2.2 kg on 20 mg of oxandrolone, 1.5 ± 2.5 kg on 40 mg of oxandrolone, and 1.8 ± 1.8 kg on 80 mg of oxandrolone (see Table 2). The increase in BCM on the

TABLE 2. Change in Body Weight and Composition at Week 12 (intent-to-treat)

		Oxandrolone		
	Placebo	20 mg	40 mg	80 mg
Weight (kg)	1.1 ± 2.7	1.8 ± 3.9	2.8 ± 3.3*	2.3 ± 2.9‖
n	64	63	64	67
BCM (kg)	0.45 ± 1.7	0.91 ± 2.2	1.5 ± 2.5†	1.8 ± 1.8‡
n	62	61	59	64
Intracellular water (L)	0.4 ± 1.6	0.8 ± 2.0	1.4 ± 2.3†	1.7 ± 1.6‡
n	62	61	59	64
Extracellular water (L)	0.3 ± 1.5	0.4 ± 2.9	0.2 ± 1.3	−0.2 ± 1.5
n	62	61	59	64
Body fat (kg)	0.3 ± 1.6	0.4 ± 2.2	1.0 ± 2.4§	0.6 ± 1.8
n	62	61	59	64

**P* = 0.004 vs. placebo.
†*P* = 0.0049 vs. placebo.
‡*P* = 0.0002 vs. placebo.
§*P* = 0.0444 vs. placebo.
‖*P* = 0.0450 vs. placebo.

40-mg and 80-mg doses at 12 weeks was significantly greater than that on placebo ($P = 0.0049$ and $P = 0.0002$, respectively). Similar results were obtained when intracellular water was analyzed by BIA (see Table 2). In contrast, there were no significant changes in extracellular water in any group (see Table 2). There was also a trend to gain body fat on the 40-mg dose, but this did not reach statistical significance using the multiple comparisons criteria.

The entry criteria included 10% to 20% of unintentional loss of weight or a BMI ≤20 kg/m^2. These criteria allowed patients who were over their ideal body weight or even obese at baseline to enter the study if they had lost 10% to 20% of their body weight. Five subjects were obese (>120% ideal body weight), with the highest weight at entry being 107 kg. Twenty-four percent of the patients had a BMI >22.5 kg/m^2. Therefore, we performed post hoc analysis evaluating changes in body weight and composition in subjects with a BMI ≤22.5 kg/m^2 on an intent-to-treat basis at 12 weeks or last measurement. Their weight increase over baseline at 12 weeks was 0.8 ± 2.7 kg on placebo, 2.7 ± 4.0 kg on 20 mg of oxandrolone, 2.9 ± 2.6 kg on 40 mg of oxandrolone, and 2.5 ± 2.8 kg on 80 mg of oxandrolone (all significantly increased over baseline). Compared with placebo, subjects receiving 20 mg, 40 mg, or 80 mg of oxandrolone had significantly higher weights at week 12 ($P = 0.0026$, $P = 0.0005$, and $P = 0.0041$, respectively). Similar changes were found for BCM, where the increases at 12 weeks over baseline were 0.2 ± 1.5 kg in the placebo group, 1.1 ± 2.1 in the 20-mg oxandrolone group; 1.8 ± 1.5 kg in the 40-mg oxandrolone group, and 2.0 ± 1.7 kg in the 80-mg oxandrolone group. Compared with placebo, subjects receiving 20, 40, or 80 mg of oxandrolone had a significantly higher BCM at week 12 ($P = 0.0122$, $P < 0.0001$, and $P < 0.0001$, respectively).

Functional Outcomes

No significant differences were seen in MOS HIV health surveys for any treatment group. There was no significant change from baseline in total work output in the

subset of subjects who underwent treadmill testing in any treatment group. There was no correlation between change in weight and QOL score or total work output.

Safety

Neither HIV RNA by RT-PCR nor $CD4^+$ lymphocyte count was significantly affected by oxandrolone (Table 3). There were no significant changes in hemoglobin and white blood cell counts. However, there was a dose-dependent increase in platelet count ($P < 0.017$ for all doses of oxandrolone vs. placebo). There were small but significant increases in levels of creatinine and creatine kinase but not in blood urea nitrogen (BUN) in the oxandrolone groups compared with the placebo group.

Serum albumin, total protein, bilirubin, alkaline phosphatase, lactate dehydrogenase (LDH), and gamma-glutamyl transferase (GGT) levels were not significantly changed (see Table 3). However, there were dose-dependent increases in AST and ALT appearing by the first 4 to 8 weeks of therapy. The increase in AST was significant at the 80-mg dose compared with baseline, whereas the increase in ALT was significant at the 40-mg and 80-mg doses. Furthermore, there was a dose-related increase in the incidence of WHO grade III and IV liver toxicity for ALT and AST with increasing dose of oxandrolone (Table 4). For AST, WHO grade III and IV toxicity occurred in 2 of 61 subjects on placebo, 2 of 60 on 20 mg of oxandrolone, 6 of 61 on 40 mg of oxandrolone, and 9 of 61 on 80 mg of oxandrolone. For ALT, WHO grade III and IV toxicity occurred in 1 of 61 subjects on placebo, 3 of 60 on 20 mg of oxandrolone, 7 of 61 on 40 mg of oxandrolone, and 9 of 61 on 80 mg of oxandrolone (for trend, $P = 0.0047$). Three subjects receiving the 40-mg dose and 4 subjects receiving the 80-mg dose were discontinued from the drug because of laboratory abnormalities.

Glucose, triglyceride, and total cholesterol levels in patients receiving oxandrolone were not significantly different from those receiving placebo (see Table 3). There was a significant decrease in uric acid and plasma high-density lipoprotein (HDL) cholesterol levels at all doses. Furthermore, there was a significant increase in low-density lipoprotein (LDL) cholesterol levels at the 40-mg and 80-mg doses.

TABLE 3. Safety Markers

			Oxandrolone		
		Placebo	20 mg	40 mg	80 mg
HIV RNA by PCR (μL)	Baseline	204,915 ± 581,530	154,294 ± 377,496	156,563 ± 376,248	123,994 ± 391,468
	change week 12	−110,419 ± 654,209	1338 ± 734,313	−81,152 ± 297,702	−83,976 ± 346,641
$CD4^+$ T lymphocyte count (%)	Baseline	15.5 ± 10.1	14.9 ± 11.2	16.8 ± 11.4	15.1 ± 9.9
	change week 12	0.2 ± 4.1	1.4 ± 3.9	1.1 ± 5.3	0.8 ± 3.1
Hemoglobin (g/L)	Baseline	137 ± 20	137 ± 20	134 ± 19	137 ± 16
	change week 12	5 ± 15	−4 ± 13	−2 ± 14	−3 ± 15
Platelets (10^9/L)	Baseline	221 ± 90.0	217 ± 67.2	228 ± 77.6	235 ± 70.6
	change week 12	3.1 ± 53.9	49.6 ± 86.7*	51.3 ± 103*	64.9 ± 59.1*
Creatinine (μmol/L)	Baseline	79.6 ± 17.7	79.6 ± 17.7	70.7 ± 17.7	79.6 ± 26.5
	change week 12	0.0 ± 17.7	8.8 ± 26.5*	17.7 ± 26.5*	17.7 ± 17.7*
Creatinine kinase (U/L)	Baseline	192 ± 393	138 ± 220	114 ± 81	167 ± 217
	change week 12	−61 ± 424	58 ± 94*	88 ± 127*	70 ± 234*
AST (U/L)	Baseline	42.4 ± 24.7	39.9 ± 22.0	36.6 ± 20.8	39.5 ± 22.4
	change week 12	−2.6 ± 37.0	3.6 ± 23.8	12.1 ± 56.7	20.3 ± 38.3*
ALT (U/L)	Baseline	39.4 ± 27.2	42.7 ± 33.1	37.0 ± 28.5	40.1 ± 30.4
	change week 12	−1.6 ± 39.3	4.4 ± 38.3	19.2 ± 56.3*	37.5 ± 61.0*
Glucose (mmol/L)	Baseline	5.2 ± 1.5	5.1 ± 1.1	4.9 ± 1.0	5.1 ± 0.9
	change week 12	0.1 ± 1.0	0.1 ± 1.8	0.6 ± 2.4	0.1 ± 1.3*
Uric acid (μmol/L)	Baseline	345 ± 95	339 ± 83	357 ± 107	333 ± 71
	change week 12	−12 ± 71	−54 ± 71*	−54 ± 101*	−77 ± 59*
Triglycerides (mmol/L)	Baseline	2.78 ± 2.99	3.99 ± 8.44	3.65 ± 4.90	2.28 ± 1.89
	change week 12	0.09 ± 2.01	−1.33 ± 7.10	−0.63 ± 2.96	0.12 ± 1.10
Cholesterol (mmol/L)	Baseline	4.6 ± 1.6	4.9 ± 2.9	4.6 ± 1.5	4.6 ± 1.3
	change week 12	0.01 ± 1.0	−0.3 ± 2.4	0.4 ± 1.6	0.3 ± 1.2
LDL (mmol/L)	Baseline	2.8 ± 1.3	2.7 ± 1.1	2.6 ± 0.8	2.6 ± 0.8
	change week 12	0.1 ± 1.0	0.4 ± 1.3	0.7 ± 1.3*	0.8 ± 1.1*
HDL (mmol/L)	Baseline	1.0 ± 0.4	1.0 ± 0.4	0.9 ± 0.3	1.0 ± 0.4
	change week 12	−0.03 ± 0.3	−0.3 ± 0.3*	−0.3 ± 0.3*	−0.5 ± 0.4*
Lp(a) (mmol/L)	Baseline	0.7 ± 0.7	0.9 ± 1.0	0.5 ± 0.5	0.7 ± 0.8
	change week 12	0.2 ± 0.7	−0.2 ± 0.4	−0.2 ± 0.5*	−0.6 ± 0.7*

Values are mean ± SD.
*$P < 0.017$ vs. placebo.
Lp(a) indicates lipoprotein (a).

TABLE 4. Grade III or IV Toxicities and Reasons for Discontinuation

		Oxandrolone			
	Placebo	20 mg	40 mg	80 mg	Total
Grade III or IV toxicities					
AST	2	2	6	9*	19
ALT	1	3	7†	9‡	20§
Total bilirubin	1	0	0	1	2
LDH	0	0	0	1	1
Uric acid	0	0	0	1	1
Total grade III or IV toxicities	4	5	13	21	43
Reasons for discontinuation					
Adverse experience or abnormal laboratory tests	3	1	7	9	20
Noncompliance with protocol requirements	4	6	6	2	18
Voluntary patient withdrawal or requested removal	2	2	2	3	9
Patient moved or lost to follow-up	1	3	1	2	7
Death	1	3	1	1	6
Lack of efficacy	1	2	1	1	5
Intercurrent medical problem or disease and related complications	0	1	0	1	2
Total reasons for discontinuation	12	18	18	19	67

*$P = 0.054$ vs. placebo.
†$P = 0.067$ vs. placebo.
‡$P = 0.021$ vs. placebo.
§Dose trend, $P = 0.0047$.

Six patents died during the placebo-controlled study (see Table 4), and 3 more died during the open-label phase or within 30 days of last receiving study medication during the placebo-controlled phase. Of the 9 subjects who died, 2 were on placebo, 3 were on 20 mg of oxandrolone, 2 were on 40 mg of oxandrolone, and 2 were on 80 mg of oxandrolone. There were no significant differences between the treatment groups in the numbers of infections, serious adverse events (SAEs), or milder adverse events. Seven SAEs were reported in 6 subjects on placebo, 20 SAEs were reported in 13 subjects on 20 mg of oxandrolone, 24 SAEs were reported in 14 subjects on 40 mg of oxandrolone, and 20 SAEs were reported in 14 subjects on 80 mg of oxandrolone. One hundred eighty-one different types of infections and adverse events were reported.

Overall dropout rates were similar among treatment groups (see Table 4). In some subjects, treatment discontinuation was prompted by more than 1 reason. There was a trend toward increased dropout because of an adverse experience or abnormal laboratory test results in the 40-mg and 80-mg oxandrolone groups attributable to treatment discontinuation for WHO grade III and IV elevations in AST and ALT.

Gonadal-Pituitary Function

Baseline total testosterone levels averaged close to the lower limits of normal (270 ng/dL; Table 5). At 12 weeks, serum LH and FSH concentrations decreased significantly from baseline in all oxandrolone-treated groups, consistent with an androgenic action. Serum SHBG concentrations also decreased with increasing doses of oxandrolone, which also suggests an androgenic effect of oxandrolone (SHBG was determined in a subset of patients, and total testosterone levels in the subset were similar to those in the larger cohort; data not shown).

Total and free testosterone concentrations measured by direct RIA did not show a dose-related change. We used celite chromatography to separate testosterone from oxandrolone before RIA and found that serum total testosterone concentrations were significantly decreased from baseline at all doses of oxandrolone but not with placebo treatment (see Table 5).

Open-Label Study

After the double-blind placebo-controlled study, a subset of subjects opted to take 20 mg of oxandrolone in an open-label study. All 4 groups receiving 20 mg of oxandrolone during this 12-week open-label phase continued to gain weight (Table 6). By the end of the open-label phase, there were no significant differences in weight gain among the groups. AST levels decreased; although AST levels remained above baseline, they were no longer significantly different from baseline (see Table 6).

DISCUSSION

Oxandrolone treatment was associated with significantly greater body weight gain above baseline than with placebo. A major portion of this weight gain occurred in the lean body compartment, as reflected in the significant gains in BCM, intracellular water, and serum creatinine levels. The gains in body weight during the double-blind phase of the study were sustained during the open-label phase of the study.

Oxandrolone administration has been shown to increase muscle protein synthesis in emaciated burn patients,[56] muscle mass and maximal voluntary strength in older men at risk for sarcopenia,[57–60] and weight in patients with cancer cachexia. Most previous studies have included small numbers of subjects, however; this study is the largest randomized placebo-controlled trial of an androgen in patients with HIV-associated weight loss.

Serum LH and FSH levels decreased significantly during oxandrolone administration, consistent with its androgenic activity. Whereas conventional measurement of testosterone did not show consistent decreases, assay after chromatographic separation did show suppression of testosterone, confirming the androgenic effect and indicating that oxandrolone or a metabolite cross-reacted in the conventional testosterone assay. This dose-ranging study did not include women; therefore, we cannot determine whether the level of androgenic activity seen with oxandrolone would have the expected detrimental virilizing effects in women.

Oxandrolone administration was generally well tolerated. Grade III and IV elevations of transaminases were observed in >5% of study participants, however, especially at the 80-mg dose. Careful monitoring of these parameters is therefore

TABLE 5. Effect of Oxandrolone on Serum LH, FSH, Total and Free Testosterone, and SHBG Levels (baseline to week 12)

		Oxandrolone		
	Placebo	20 mg	40 mg	80 mg
Testosterone by RIA (nmol/L)				
Baseline	7.7 ± 3.4	9.5 ± 4.6	9.2 ± 5.0	12.0 ± 13.6*
change week 12	2.6 ± 10.0	−1.7 ± 4.3	1.1 ± 10.0	−2.2 ± 5.6
P	0.0581	0.0120	0.4523	0.012
n	54	46	49	46
Free testosterone (pmol/L)				
Baseline	101 ± 52	118 ± 59	114 ± 52	146 ± 139*
change week 12	26 ± 109	−41 ± 55	−24 ± 86	−45 ± 51.3
P	0.0838	0.0001	0.0581	0.0001
n	54	46	49	46
LH (U/L)				
Baseline	3.52 ± 2.61	4.07 ± 4.00	3.97 ± 2.66	4.03 ± 3.05
change week 12	0.93 ± 4.68	−1.08 ± 2.33	−1.35 ± 2.90	−2.18 ±2.74
P	0.1519	0.0029	0.0020	0.0001
n	54	46	49	46
FSH (U/L)				
Baseline	5.75 ± 4.95	5.12 ± 3.81	6.08 ± 4.52	4.81 ± 4.04
change week 12	0.78 ± 2.94	−0.67 ± 3.37	−0.80 ± 3.08	−1.28 ± 2.06
P	0.0563	0.1809	0.0753	0.0001
n	54	46	49	46
SHBG (nmol/L)				
Baseline	44.8 ± 22.7	41.4 ±20.2	42.3 ± 23.4	44.2 ± 20.9
change week 12	0.43 ± 16.0	−24.4 ± 21.3	−26.8 ± 23.1	−35.0 ± 17.2
P	0.8751	0.0001	0.0001	0.0001
n	35	23	31	24
Testosterone by extraction and chromatography (ng/dL)				
Baseline	289 ± 153	269 ± 120	282 ± 117	314 ± 111
change week 12	−1.5 + 156	−124 + 129	−126 ± 126	−209 ± 122
P	0.504	0.001	0.001	0.001
n	30	32	30	33

Data are mean ± SD.

indicated after the initiation of oxandrolone therapy. Furthermore, LDL levels increased and HDL levels decreased.

There has been considerable debate about what magnitude of change in body weight is clinically meaningful. An AIDS Clinical Trial Group (ACTG) expert panel on HIV-associated wasting expressed the opinion that a gain of 1.5 kg is clinically meaningful (Fred Sattler, MD, personal communication). The average weight gain at each of the oxandrolone doses exceeded 1.5 kg, whereas the increase in the placebo group was less than 1.5 kg. Only the 40-mg dose of oxandrolone induced more than a 1.5-kg increase in weight over that attained with placebo (an increase over placebo of 1.7 kg based on a 2.8-kg increase for 40 mg of oxandrolone vs. a 1.1-kg increase for placebo). For subjects whose BMI was $\leq$22.5 kg/m^2, all 3 doses of oxandrolone induced more than a 1.5-kg increase over placebo (20 mg induced a 1.9-kg increase, 40 mg induced a 2.1-kg increase, and 80 mg induced a 1.7-kg increase). In subjects whose BMI was $\leq$22.5 kg/m^2, the mean increases in BCM in patients treated with the 40- or 80-mg dose of oxandrolone were also greater than 1.5 kg above that attained with placebo. These changes in weight and BCM compare favorably with those observed during administration of rhGH[27,28] and testosterone.[31–36] In a meta-analysis of placebo-controlled, randomized, clinical trials of testosterone, the average gain in lean body mass was 1.3 kg in testosterone-treated HIV-infected men.[61]

In spite of significant body weight gains and lean mass accretion, total work output during treadmill exercise did not significantly change during treatment. This is consistent with the growing body of data that androgenic steroids increase muscle mass but do not affect measures of endurance, such as treadmill performance.[62–64] Reports of randomized clinical trials published subsequent to the initiation of this study have reported significant gains in maximal voluntary strength with androgen supplementation of HIV-infected men with weight loss[35]; gains in muscle strength are generally proportional to increases in muscle mass.[35]

Participants in this study were able to consume a well-balanced diet at study entry as assessed by a dietitian. In developing countries of Africa and Asia, many HIV-infected patients have an overall energy deficit, with varying macro- and micronutrient deficiencies. We do not know whether

TABLE 6. Change From Baseline in Weight, AST, and ALT in Subjects Continuing in the Open-Label (20 mg) Study

		Oxandrolone		
	Placebo	20 mg	40 mg	80 mg
Weight gain (kg)				
n	53	46	48	46
Double-blind placebo phase 0 to 12 weeks	1.3 ± 3.0	2.0 ± 3.9	3.0 ± 3.3*	2.5 ± 3.0
Open-label 20-mg phase 12 to 24 weeks	1.6 ± 4.4	1.4 ± 2.5	0.3 ± 2.7	1.1 ± 3.0
Liver function tests				
n	42	40	39	38
AST Baseline to 24 weeks	6.2 ± 45.4	−1.4 ± 22.1	6.8 ± 30.2	18.4 ± 39.9
ALT Baseline to 24 weeks	7.6 ± 43.9	7.6 ± 69.3	17.4 ± 42.1	35.1 ± 70.8

*$P < 0.004$ vs. placebo.

androgen administration would be efficacious in preventing weight loss in HIV-infected patients with severe wasting or in nutritionally depleted individuals.

Administration of oxandrolone has been associated with significant decreases in plasma HDL cholesterol levels and increases in LDL cholesterol levels.[60,65,66] The administration of the 40- and 80-mg doses was associated with significant increases in ALT and AST; these increases were transient and returned toward baseline in most subjects. Treatment discontinuations attributable to persistent and marked increases in transaminases were common and occurred in more than 5% of individuals. We found no increase in bilirubin or alkaline phosphatase.

The gains in body weight and BCM were related to oxandrolone dose. Similarly, there were dose-dependent increases in AST and ALT levels and common treatment discontinuations attributable to AST and ALT elevations. Thus, the best trade-off between the anabolic effects and AST and ALT elevation was achieved at the 40-mg daily dose. The therapeutic efficacy and safety of this dose should be further evaluated in subsequent clinical trials.

The decreases in HDL and increases in LDL represent a proatherogenic lipoprotein profile. Clinicians therefore need to weigh the risk-benefit ratio of this therapy. Wasting syndrome predicts a significant risk of complications and death, but even studies as large as this one are not large enough and have not been carried out long enough to determine whether reversal of that risk occurs with treatment of wasting and to determine the risk of cardiovascular disease. The risk of atherosclerosis predicted by this lipoprotein profile suggests that such therapy should be restricted to those with significant wasting or should be terminated when wasting has improved. Mean CD4 lymphocyte counts in this study were $>200 \times 10^6$/L, which is higher than in most earlier studies of HIV-associated wasting (which often had mean values $\leq 50 \times 10^6$/L), indicating better health later in the epidemic. In that light, future studies should likely exclude those with obesity even in the presence of weight loss. In post hoc analysis, we found that the 20-mg dose was more effective in those with a BMI at entry of ≤ 22.5 kg/m^2. The lower dose was accompanied by lesser increases in LDL and transaminases. Thus, a prospective study excluding obese patients could establish that a 20-mg dose is efficacious and associated with a lower frequency of adverse events.

A number of therapies, including dronabinol, megestrol acetate,[24,25] and rhGH,[26–29] are approved for the treatment of HIV-associated wasting. Orexigenic agents, such as dronabinol and megestrol acetate, increase appetite but have not been shown to increase lean body mass. rhGH was approved for treatment of patients with HIV-associated wasting based on a trial that demonstrated increases in fat-free mass and increased performance on treadmill testing.[28] rhGH is expensive, however, and its administration is associated with adverse effects at the approved doses. Oxandrolone compares favorably with rhGH in terms of the weight and BCM gain as well as retail cost. Furthermore, oxandrolone did not reduce fat stores and is associated with a lower frequency of adverse events than rhGH. Therefore, it may be viewed as an adjunct or alternative to rhGH for the treatment of patients with HIV-associated weight loss. Of 2 recent smaller studies on the use of nandrolone, an injectable anabolic steroid, for AIDS wasting, one reported that nandrolone induced a similar gain in weight[67] to the increase seen here with oxandrolone, whereas the other found that nandrolone induced a larger gain in weight than we report with oxandrolone. Oxandrolone has the advantage of oral administration, however, which may be important in patients with loss of muscle and fat, such as occurs in AIDS wasting. Further studies are needed to determine the efficacy of oxandrolone in improving muscle strength, physical function, and health-related QOL in HIV-infected patients with weight loss.

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REFERENCES

1. Hoover DR, Saah AJ, Bacellar H, et al. Clinical manifestations of AIDS in the era of pneumocystis prophylaxis. Multicenter AIDS Cohort Study. *N Engl J Med.* 1993;329:1922–1926.
2. Weiss PJ, Wallace MR, Olson PE, et al. Changes in the mix of AIDS-defining conditions. *N Engl J Med.* 1993;329:1962.
3. Nahlen BL, Chu SY, Nwanyanwu OC, et al. HIV wasting syndrome in the United States. *AIDS.* 1993;7:183–188.
4. Wanke CA, Silva M, Knox TA, et al. Weight loss and wasting remain common complications in individuals infected with human immunodeficiency virus in the era of highly active antiretroviral therapy. *Clin Infect Dis.* 2000;31:803–805.
5. Lindan CP, Allen S, Serufilira A, et al. Predictors of mortality among HIV-infected women in Kigali, Rwanda. *Ann Intern Med.* 1992;116: 320–328.
6. Kotler DP, Tierney AR, Wang J, et al. Magnitude of body-cell-mass depletion and the timing of death from wasting in AIDS. *Am J Clin Nutr.* 1989;50:444–447.
7. Guenter P, Muurahainen N, Simons G, et al. Relationships among nutritional status, disease progression, and survival in HIV infection. *J Acquir Immune Defic Syndr Hum Retrovirol.* 1993;6: 1130–1138.
8. Suttmann U, Ockenga J, Selberg O, et al. Incidence and prognostic value of malnutrition and wasting in human immunodeficiency virus-infected outpatients. *J Acquir Immune Defic Syndr Hum Retrovirol.* 1995;8:239–246.
9. Ott M, Fischer H, Polat H, et al. Bioelectrical impedance analysis as a predictor of survival in patients with human immunodeficiency virus infection. *J Acquir Immune Defic Syndr Hum Retrovirol.* 1995;9: 20–25.
10. Palenicek JP, Graham NM, He YD, et al. Weight loss prior to clinical AIDS as a predictor of survival. Multicenter AIDS Cohort Study Investigators. *J Acquir Immune Defic Syndr Hum Retrovirol.* 1995; 10:366–373.
11. Melchior JC, Niyongabo T, Henzel D, et al. Malnutrition and wasting, immunodepression and chronic inflammation are independent predictors of survival in HIV-infected patients. *Nutrition.* 1999;15: 865–869.
12. Turner J, Muurahainen N, Graber TC, et al. Nutritional status and quality of life. Presented at: Xth International Conference on AIDS; Yokohama, Japan, 1994.
13. Cohan GR, Muurahainen N, Guenter P, et al. HIV-related hospitalization, CD4 percent and nutritional markers. Presented at: VIII International Conference on AIDS; 1992; Amsterdam.
14. Wilson IB, Roubenoff R, Knox T, et al. Relation of lean body mass to health-related quality of life in persons with HIV. *J Acquir Immune Defic Syndr.* 2000;24:137–146.
15. Wagner GJ, Ferrando SJ, Rabkin JG. Psychological and physical health correlates of body cell mass depletion among HIV+ men. *J Psychosom Res.* 2000;49:55–57.
16. Kotler DP, Wang J, Pierson RN. Body composition studies in patients with the acquired immunodeficiency syndrome. *Am J Clin Nutr.* 1985; 42:1255–1265.
17. Ott M, Lembcke B, Fischer H, et al. Early changes of body composition in human immunodeficiency virus-infected patients: tetrapolar body impedance analysis indicates significant malnutrition. *Am J Clin Nutr.* 1993;57:15–19.
18. Paton NI, Macallan DC, Jebb SA, et al. Longitudinal changes in body composition measured with a variety of methods in patients with AIDS. *J Acquir Immune Defic Syndr Hum Retrovirol.* 1997;14: 119–127.
19. Mulligan K, Tai VW, Schambelan M. Cross-sectional and longitudinal evaluation of body composition in men with HIV infection. *J Acquir Immune Defic Syndr Hum Retrovirol.* 1997;15:43–48.
20. Grinspoon S, Corcoran C, Miller K, et al. Body composition and endocrine function in women with acquired immunodeficiency syndrome. *J Clin Endocrinol Metab.* 1997;82:1332–1337.
21. Swanson B, Hershow RC, Sha BE, et al. Body composition in HIV-infected women. *Nutrition.* 2000;16:1064–1068.
22. Kotler DP, Tierney AR, Culpepper-Morgan JA, et al. Effect of home total parenteral nutrition on body composition in patients with acquired immunodeficiency syndrome. *JPRN J Parenter Enteral Nutr.* 1990; 14:454–458.
23. Kotler DP, Tierney AR, Ferraro R, et al. Enteral alimentation and repletion of body cell mass in malnourished patients with acquired immunodeficiency syndrome. *Am J Clin Nutr.* 1991;53:149–154.
24. Von Roenn JH, Armstrong D, Kotler DP, et al. Megestrol acetate in patients with AIDS-related cachexia. *Ann Intern Med.* 1994;121: 393–399.
25. Oster MH, Enders SR, Samuels SJ, et al. Megestrol acetate in patients with AIDS and cachexia. *Ann Intern Med.* 1994;121:400–408.
26. Mulligan K, Grunfeld C, Hellerstein MK, et al. Anabolic effects of recombinant human growth hormone in patients with wasting associated with human immunodeficiency virus infection. *J Clin Endocrinol Metab.* 1993;77:956–962.
27. Krentz AJ, Koster FT, Crist DM, et al. Anthropometric, metabolic, and immunological effects of recombinant human growth hormone in AIDS and AIDS-related complex. *J Acquir Immune Defic Syndr Hum Retrovirol.* 1993;6:245–251.
28. Schambelan M, Mulligan K, Grunfeld C, et al. Recombinant human growth hormone in patients with HIV-associated wasting. A randomized, placebo-controlled trial. Serostim Study Group [see comments]. *Ann Intern Med.* 1996;125:873–882.
29. Moyle GJ, Daar E, Gertner J, et al. Growth hormone improves lean body mass, physical performance and quality of life in subjects with HIV-associated weight loss or wasting on highly active antiretroviral therapy. *J Acquir Immune Defic Syndr.* 2004;35:367–375.
30. Coodley GO, Coodley MK. A trial of testosterone therapy for HIV-associated weight loss. *AIDS.* 1997;11:1347–1352.
31. Grinspoon S, Corcoran C, Askari H, et al. Effects of androgen administration in men with the AIDS wasting syndrome. A randomized, double-blind, placebo-controlled trial. *Ann Intern Med.* 1998; 129:18–26.
32. Bhasin S, Storer TW, Asbel-Sethi N, et al. Effects of testosterone replacement with a nongenital, transdermal system, Androderm, in human immunodeficiency virus-infected men with low testosterone levels. *J Clin Endocrinol Metab.* 1998;83:3155–3162.
33. Dobs AS, Cofrancesco J, Nolten WE, et al. The use of a transscrotal testosterone delivery system in the treatment of patients with weight loss related to human immunodeficiency virus infection. *Am J Med.* 1999;107:126–132.
34. Grinspoon S, Corcoran C, Anderson E, et al. Sustained anabolic effects of long-term androgen administration in men with AIDS wasting. *Clin Infect Dis.* 1999;28:634–636.
35. Bhasin S, Storer TW, Javanbakht M, et al. Testosterone replacement and resistance exercise in HIV-infected men with weight loss and low testosterone levels. *JAMA.* 2000;283:763–770.
36. Grinspoon S, Corcoran C, Parlman K, et al. Effects of testosterone and progressive resistance training in eugonadal men with AIDS wasting. A randomized, controlled trial. *Ann Intern Med.* 2000;133: 348–355.
37. Fairfield WP, Treat M, Rosenthal DI, et al. Effects of testosterone and exercise on muscle leanness in eugonadal men with AIDS wasting. *J Appl Physiol.* 2001;90:2166–2171.
38. Mendenhall CL, Anderson S, Garcia-Pont P, et al. Short-term and long-term survival in patients with alcoholic hepatitis treated with oxandrolone and prednisolone. *N Engl J Med.* 1984;311:1464–1470.
39. Chlebowski RT, Herrold J, Ali I, et al. Influence of nandrolone decanoate on weight loss in advanced non-small cell lung cancer. *Cancer.* 1986;58:183–186.
40. Mendenhall CL, Moritz TE, Roselle GA, et al. A study of oral nutritional support with oxandrolone in malnourished patients with alcoholic hepatitis: results of a Department of Veterans Affairs cooperative study. *Hepatology.* 1993;17:564–576.
41. Demling RH, Orgill DP. The anticatabolic and wound healing effects of the testosterone analog oxandrolone after severe burn injury. *J Crit Care.* 2000;15:12–17.
42. Orr R, Fiatarone Singh M. The anabolic androgen oxandrolone in the treatment of wasting and catabolic disorders: review of efficacy and safety. *Drugs.* 2004;64:725–750.
43. Berger JR, Pall L, Winfield D. Effect of anabolic steroids on HIV-related wasting myopathy. *J South Med.* 1993;86:865–866.
44. Gold J, High HA, Li Y, et al. Safety and efficacy of nandrolone decanoate for treatment of wasting in patients with HIV infection. *AIDS.* 1996;10:745–752.

45. Berger JR, Pall L, Hall CD, et al. Oxandrolone in AIDS-wasting myopathy. *AIDS*. 1996;10:1657–1662.
46. Strawford A, Barbieri T, Neese R, et al. Effects of nandrolone decanoate therapy in borderline hypogonadal men with HIV-associated weight loss. *J Acquir Immune Defic Syndr*. 1999;20:137–146.
47. Strawford A, Barbieri T, Van Loan M, et al. Resistance exercise and supraphysiologic androgen therapy in eugonadal men with HIV-related weight loss: a randomized controlled trial. *JAMA*. 1999;281:1282–1290.
48. Sattler FR, Jaque SV, Schroeder ET, et al. Effects of pharmacological doses of nandrolone decanoate and progressive resistance training in immunodeficient patients infected with human immunodeficiency virus. *J Clin Endocrinol Metab*. 1999;84:1268–1276.
49. Batterham MJ, Garsia R. A comparison of megestrol acetate, nandrolone decanoate and dietary counselling for HIV associated weight loss. *Int J Androl*. 2001;24:232–240.
50. Earthman CP, Reid PM, Harper IT, et al. Body cell mass repletion and improved quality of life in HIV-infected individuals receiving oxandrolone. *JPEN J Parenter Enteral Nutr*. 2002;26:357–365.
51. Hengge UR, Stocks K, Wiehler H, et al. Double-blind, randomized, placebo-controlled phase III trial of oxymetholone for treatment of HIV wasting. *AIDS*. 2003;17:699–710.
52. Wu AW, Rubin HR, Mathews WC, et al. A health status questionnaire using 30 items from the Medical Outcomes Study. Preliminary validation in persons with early HIV infection. *Med Care*. 1991;29:786–798.
53. Bhasin S, Storer TW, Berman N, et al. The effects of supraphysiologic doses of testosterone on muscle size and strength in normal men. *N Engl J Med*. 1996;335:1–7.
54. Sinha-Hikim I, Arver S, Beall G, et al. The use of a sensitive equilibrium dialysis method for the measurement of free testosterone levels in healthy, cycling women and in human immunodeficiency virus-infected women. *J Clin Endocrinol Metab*. 1998;83:1312–1318.
55. Choi HH, Gray P, Calof O, et al. The effects of testosterone replacement in HIV-infected women with weight loss. *J Clin Endocrinol Metab*. 2005;90:1531–1541.
56. Wolf SE, Thomas SJ, Dasu MR, et al. Improved net protein balance, lean mass, and gene expression changes with oxandrolone treatment in the severely burned. *Ann Surg*. 2003;237:801–810.
57. Sheffield-Moore M, Wolfe RR, Gore DC, et al. Combined effects of hyperaminoacidemia and oxandrolone on skeletal muscle protein synthesis. *Am J Physiol Endocrinol Metab*. 2000;278:E273–E279.
58. Sheffield-Moore M, Urban RJ, Wolf SE, et al. Short-term oxandrolone administration stimulates net muscle protein synthesis in young men. *J Clin Endocrinol Metab*. 1999;84:2705–2711.
59. Schroeder ET, Zheng L, Ong MD, et al. Effects of androgen therapy on adipose tissue and metabolism in older men. *J Clin Endocrinol Metab*. 2004;89:4863–4872.
60. Schroeder ET, Zheng L, Yarasheski KE, et al. Treatment with oxandrolone and the durability of effects in older men. *J Appl Physiol*. 2004;96:1055–1062. [Epub 2003 Oct 24].
61. Kong A, Edmonds P. Testosterone therapy in HIV wasting syndrome: systematic review and meta-analysis. *Lancet Infect Dis*. 2002;2:692–699.
62. Bhasin S, Woodhouse L, Casaburi R, et al. Testosterone dose-response relationships in healthy young men. *Am J Physiol Endocrinol Metab*. 2001;281:E1172–E1181.
63. Bhasin S, Woodhouse L, Casaburi R, et al. Older men are as responsive as young men to the anabolic effects of graded doses of testosterone on the skeletal muscle. *J Clin Endocrinol Metab*. 2004;Nov 23. [Epub ahead of print].
64. Storer TW, Magliano L, Woodhouse L, et al. Testosterone dose-dependently increases maximal voluntary strength and leg power, but does not affect fatigability or specific tension. *J Clin Endocrinol Metab*. 2003;88:1478–1485.
65. Hickson RC, Ball KL, Falduto MT. Adverse effects of anabolic steroids. *Med Toxicol Adverse Drug Exp*. 1989;4:254–271.
66. Ishak KG, Zimmerman HJ. Hepatotoxic effects of the anabolic/androgenic steroids. *Semin Liver Dis*. 1987;7:230–236.
67. Storer TW, Woodhouse LJ, Sattler F, et al. A randomized, placebo-controlled trial of nandrolone decanoate in human immunodeficiency virus-infected men with mild to moderate weight loss with recombinant human growth hormone as active reference treatment. *J Clin Endocrinol Metab*. 2005;90:4474–4482. [Epub 2005 May 24].
68. Mulligan K, Zackin R, Clark RA, et al. AIDS Clinical Trials Group 329 Study Team; National Institute of Allergy and Infectious Diseases Adult AIDS Clinical Trials Group. Effect of nandrolone decanoate therapy on weight and lean body mass in HIV-infected women with weight loss: a randomized, double-blind, placebo-controlled, multicenter trial. *Arch Intern Med*. 2005;165:578–585.

APPENDIX

The following individuals were participants in the Oxandrolone Study Group:

Victor Beer, MD, Beer Medical Group, 5901 West Olympic Boulevard, Suite 505, Los Angeles, CA 90036

Daniel Berger, MD, Center for Special Immunology, 2835 North Sheffield Avenue, Suite 104, Chicago, IL 60657

Shalender Bhasin, MD, Charles R. Drew University of Medicine and Science, 1621 East 120th Street, MP-02, Los Angeles, CA 90059

Eric S. Daar, MD, Cedars-Sinai Medical Center, 8700 Beverly Boulevard, B217, Los Angeles, CA 90048

Douglas Dieterich, MD, Liberty Medical, LLP, 345 East 37th Street, Suite 306, New York, NY 10016

Adrian S. Dobs, MD, Johns Hopkins University, Department of Endocrinology and Metabolism, Blalock 906, 600 North Wolfe Street; Baltimore, MD 21287–4904

Richard Elion, MD, Community Care Center, 1737 20th Street NW, Washington, DC 20009

Jeffrey Fessel, MD, Kaiser Permanente Medical Center, HIV Research Unit, 4141 Geary Boulevard, Room 221, San Francisco, CA 94115

Marshall J. Glesby, MD, Community Research Initiative on AIDS, 230 West 38th Street, 17th Floor, New York, NY10018

Carl Grunfeld, MD, PhD, University of California at San Francisco, Metabolism Section (111F), and Department of Veterans Affairs Medical Center, 4150 Clement Street, San Francisco, CA 94121

Barbara Johnston, MD, St. Vincent's Hospital and Medical Center, 36 Seventh Avenue, Suite 415, New York, NY 10011

Donald Kotler, MD, St. Luke's–Roosevelt Hospital Center, Gastrointestinal Immunology S&R 1301, 1111 Amsterdam Avenue, New York, NY 10025.

Craig A. Lindquist, MD, PhD, Marin County Specialty Clinic, 161 Mitchell Boulevard, Suite 200, San Rafael, CA 94903

Alvin E. Fisher, MD, Omega Medical Research, 400 Reservoir Avenue, Suite LL 1J, Providence, RI 02907

Jeff P. Nadler, MD, University of South Florida, Division of Infectious Disease Center, 12901 North 30th Street, Box 19, Tampa, FL 33612

Dorece Norris, MD, Center for Quality Care, 508 South Habana Avenue, Suite 240, Tampa, FL 33609

Richard Pollard, MD, University of Texas Medical Branch at Galveston, 301 University Boulevard, Suite 722, Galveston, TX 77555–0882

Peter Shalit, MD, 600 Broadway, Suite 420, Seattle, WA 98122

Daniel Skiest, MD, University of Texas Southwestern Medical Center at Dallas, Division of Infectious Diseases, 5323 Harry Hines Boulevard, Dallas, TX 75235

Paul Skolnik, MD, Division of Geographic Medicine and Infectious Diseases, New England Medical Center, 750 Washington Street, NEMC 67, Boston, MA 02111

James Sosman, MD, HIV Program, University of Wisconsin, J5/215 CSC, 600 Highland Avenue, Madison, WI 53792

Corklin Steinhart, MD, Special Immunology Services/Mercy Hospital, Steinhart Medical Group, 3569 South Miami Avenue, Suite 4006, Miami, FL 33133

James H. Von Roenn, MD, Northwestern University, Hematology/Oncology Division, 233 East Erie, Suite 700, Chicago, IL 60611